

### **REMARKS**

Claims 35 to 53 are pending, with claim 37 withdrawn from consideration as allegedly drawn to a non-elected invention. Thus, claims 35, 36 and 38 to 53 are presently under examination.

#### ***Regarding the amendments***

The claim dependency of multiply dependent claims 39 and 40 has been amended such that the claims now depend from claims 35 and 36 rather than claims 35, 36 and 37. The amendment to claims 39 and 40 does not add new matter. Accordingly, Applicants respectfully request that the Examiner enter the amendment.

#### ***Regarding Objections to the Drawings***

The drawings stand objected to as indicated in paragraph 5 of the Office Action mailed September 23, 2003. Corrected formal drawings for Figures 1 through 7 are submitted herewith. The formal drawings comply with the objections stated in the Notice of Draftperson's Patent Drawing Review dated September 8, 2003. Accordingly, Applicants respectfully request that the objection to the specification be withdrawn.

#### ***Regarding Objections to the Claims***

The Examiner has maintained the objection to claims 39 and 40 as allegedly depending on 37, which has been withdrawn from consideration as allegedly drawn to a non-elected invention. While maintaining that claim 37 should ultimately be rejoined with the elected subject matter, Applicants herein amend claims 39 and 40 such that they no longer depend from claim 37.

***Regarding the double patenting rejections***

The provisional rejection of claims 35, 36, 38, 39, 41, 42, 44, 45, 47, 48 and 53 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 61 to 63, 67, 71 to 74, and 76 to 82 of U.S. application Serial No. 10/261,161 is respectfully traversed. Applicants again respectfully defer responding to this provisional rejection until allowable subject matter has been indicated.

***Regarding the rejection under 35 U.S.C. §103***

The rejection of claims 35 to 53 under 35 U.S.C. §103(a) as allegedly obvious over Schmidt and Bostian (U.S. Patent No. 5,965,699) in view of Clegg, Curr. Opin. in Biotech. 6:103-110 (1995), respectfully is traversed.

Applicants submit that the claimed methods are unobvious over Schmidt and Bostian in view of Clegg. Specifically, Schmidt and Bostian describe a method of labeling BoNT/A cleavage product for quantitation of BoNT/A but, neither alone nor in combination with Clegg, teach or suggest resonance energy transfer assays for determining protease activity of BoNT/A or BoNT/E. At best, Schmidt and Bostian report a blocked 17-mer BoNT/A peptide substrate and the use of a fluorescamine label for detection of free amino groups on toxin cleavage product. The Office Action acknowledges that Schmidt and Bostian do not teach or suggest assaying BoNT/A activity using fluorescence resonance energy transfer (FRET) as claimed. The Office Action indicates that Clegg generally reports the use of fluorescence resonance energy transfer assays to study enzymes, and emphasizes the general benefits of FRET assays. The Office Action further asserts that one skilled in the art would have been motivated to modify the assay of Schmidt and Bostian in view of the reported advantages of FRET assays set forth in the review by Clegg.

Applicants submit that the general statements in Clegg would not have motivated one skilled in the art to modify the Schmidt and Bostian substrate to include a FRET donor fluorophore and an acceptor. According to the Examiner, one of ordinary skill in the art would have been motivated by the teachings of Clegg that FRET assays can be exploited for fluorometric enzyme assays. In this regard, the Examiner indicates that

“the motivation to modify the assay of Schmidt by incorporating FRET comes from the teaching of Clegg ‘The benefits of fluorescence resonance energy transfer are becoming increasingly evident to researchers who require measurements with high sensitivity, specificity, noninvasiveness, rapidity and relative simplicity’” (Office Action at page 5, penultimate paragraph).

As discussed further below, Applicants submit that the benefits of FRET emphasized by Clegg were already present in the assay of Schmidt and Bostian. Thus, one skilled in the art would not have been motivated to modify the assay of Schmidt and Bostian in view of the cited Clegg publication.

Applicants discuss in turn each of the five purported advantages of fluorescence resonance energy transfer assays set forth in Clegg. Firstly, in regard to assay sensitivity, Schmidt and Bostian indicate at column 2, lines 39-40, that their “[a]ssays are very sensitive (2 to 5 nanograms per milliliter toxin can be detected).” Secondly, in regard to the specificity of a clostridial toxin assay, one skilled in the art understands that assay specificity will be determined by the recognition sequence of the substrate. Thus, a FRET assay performed with the synthetic 17-mer substrate of Schmidt and Bostian modified to include a donor fluorophore and acceptor would not be expected to have increased specificity and cannot serve as a motivation to modify the assay. Thirdly, the assay of Schmidt and Bostian, which is performed *in vitro*, is noninvasive. One skilled in the art therefore would not have been motivated to modify the substrate of Schmidt and Bostian in order to produce a non-invasive assay. Fourthly and fifthly, the assay of Schmidt and Bostian is reported to be rapid and relatively simple. As stated in the 5,965,699 patent, the Schmidt and Bostian assay can be performed “in one hour or less since no separation of hydrolysis products is needed (column 2, lines 24-26; see, also, column 2, lines 39-

44; column 4, lines 23-26). In sum, one skilled in the art understands that the Schmidt and Bostian assay has high sensitivity, specificity, noninvasiveness, rapidity and relative simplicity. Thus, these general benefits of FRET as provided by Clegg would not have been sufficient to motivate one skilled in the art to modify the Schmidt and Bostian fluorescamine labeling assay.

Applicants further respectfully point out to the Examiner that the cited 1995 review by Clegg was available at the time the cited Schmidt and Bostian patent application was filed (1996). Thus, any suggestions in Clegg were already available to Schmidt and Bostian at the time they filed on their fluorescamine-based (non-FRET) assay. Clearly, the general advantages of FRET described in the Clegg review, which were available when Schmidt and Bostian filed their patent application, were not enough to motivate Schmidt and Bostian to develop a FRET-based assay in place of their assay, in which fluorescamine is used to label cleaved product. Thus, the claimed methods are unobvious over the combination of the cited references.

In view of the above remarks, Applicants submit that the claimed methods are unobvious over the combination of Schmidt and Bostian in view of Clegg. Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 35 to 53 under 35 U.S.C. § 103.

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### CONCLUSION

Applicants respectfully request that the Examiner reconsider and remove the outstanding objections and rejections. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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